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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/779,560	02/09/2001	Marianne Harboe	58982.000002	6162

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/19/2002

11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/779,560	HARBOE, MARIANNE	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *33 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32 and 35-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

Claims 1-39 are pending in the application.

Applicants' amendment to the specification and claims 1-6, 8, 10, 11, 19-21, 23, 24, 26-29, 31, and 32 and addition of claims 35-39 in Paper No. 9, filed 10/09/02, is acknowledged.

Receipt of a Declaration under 37 CFR 1.132 by inventor Peter Budtz, filed as Paper No. 10, is acknowledged.

Claims 33 and 34 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Applicants' arguments filed in Paper No. 9 and Declaration filed as Paper No. 10 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objections

1. Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 limits the desired polypeptide to having enzymatic activity. However, the desired polypeptides as recited in claim 7 are not limited to having enzymatic activity.

Claim Rejections - 35 USC § 112, Second Paragraph

2. The rejection of claim 1 (claims 4-32 and 35-39 dependent therefrom) as being confusing is maintained. While the claim has been amended to indicate the desired polypeptide has enzymatic activity prior to treatment at a pH <2.0, it remains unclear as to whether the desired polypeptide maintains

activity during and/or after treatment at a pH <2.0. As previously stated, it appears from the specification (for example, page 4, lines 26-29) and claims 2 and 3 that the desired polypeptide maintains enzymatic activity upon treatment of the medium at pH <2.0. It is suggested that applicants clarify the meaning of the claim.

3. Claim 7 is confusing in that the desired polypeptide of claim 1 has enzymatic activity, however, one of skill in the art recognizes that not all antibodies, antigens, and pharmaceutically active polypeptides have enzymatic activity. It is suggested that applicants clarify the meaning of the claim. This rejection is necessitated by amendment.

4. In view of applicants definition of the term "derived" to limit the term to "obtaining from a source of origin", the rejection of claims 20, 21 (claims 22-26 dependent therefrom), 27 (claims 28 and 30 dependent therefrom), 29 (claim 30 dependent therefrom), 31, and 32 as being indefinite in the recitation of "derived" is withdrawn.

Claim Rejections - 35 USC § 112, First Paragraph

5. The written description rejection of claim 32 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action. Claim 32, as amended, is drawn to a method of providing a polypeptide preparation comprising at least one desired polypeptide having aspartic protease enzymatic activity derived from a naturally produced aspartic protease by the addition, deletion, or substitution of one or more amino acids. Applicants argue (beginning at page 7 of Paper No. 9) the specification adequately describes the genus of variant polypeptides having aspartic protease activity. Applicants argue that numerous organisms from which the aspartic protease polypeptide may be isolated have been described in the specification and that various species of a variant aspartic protease polypeptide have been described in Examples 1 and 2. Applicants' argument is not found persuasive. The specification does not adequately describe the recited genus of polypeptides having aspartic protease enzymatic activity derived from a naturally produced aspartic protease by the addition, deletion, or substitution of one or more amino acids. Such variant aspartic proteases are an essential feature of the

claimed invention and should be described by structure or other relevant identifying characteristics. The recitation of a solely functional characteristic of the recited genus of aspartic protease variants is not sufficient to adequately describe the genus. Furthermore, as the structures of the species encompassed within the genus of recited aspartic protease variants are widely variable, the specification should disclose a representative number of structures of the recited aspartic protease variants. What constitutes a "representative number" is inversely related to the skill and knowledge in the art. At the time of the invention, a skilled artisan was yet to have the ability to divine mutations within a polypeptide's amino acid sequence that would result in a functional polypeptide having activity at a pH <2.0. The specification does not disclose even a single structure of an aspartic protease derived from a naturally produced aspartic protease by the addition, deletion, or substitution of one or more amino acids. Therefore, the genus of recited aspartic protease variants have not been adequately described in the specification.

6. The scope of enablement rejection of original claims 1-32 and newly added claims 35-39 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action. Applicants argue (beginning at page 8 of Paper No. 9) the scope of enablement provided by the instant specification is broader than stated in the Office action of Paper No. 8 and provides various examples in support thereof. Applicants argue the working examples provided in the specification together with generic disclosure in the remainder of the specification allegedly instruct a skilled artisan how to make the invention. Applicants have submitted a Declaration under 37 CFR 1.132 in support of their argument. Applicants' argument is not found persuasive. Undue experimentation would be required for a skilled artisan to make the invention in light of the enablement provided by the instant specification. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). The claims remain rejected because the specification does not provide an enabling

disclosure to inactivate any undesired protein from a desired protein as encompassed by the claims. The combination of proteins, i.e., a desired protein and an undesired protein, must be such that the desired protein maintains activity at a pH <2.0, and the undesired protein becomes at least partially inactive at a pH <2.0. Furthermore, the proteins must be submitted to a pH <2.0 for a time sufficient to at least partially inactivate the undesired protein. The Factors, as they apply to the instant rejection are addressed below.

The specification does not provide sufficient guidance and working examples to enable the scope of the claimed invention. The specification provides only three working examples of the claimed invention. The first working example provides guidance for partial inactivation of glucoamylase activity in a recombinant preparation of chymosin. The second example provides guidance for partial inactivation of glucoamylase, peptidase, amylase, cellulase, phosphatase, and protease enzymatic activities in a recombinant preparation of chymosin. The third example provides guidance for partial inactivation of glucoamylase and amylase enzymatic activities in commercial preparations of rennet (whose active ingredient is chymosin) and a recombinant chymosin. Therefore, the three working examples provide guidance only for inactivation of glucoamylase, peptidase, amylase, cellulase, phosphatase, and protease enzymatic activities in a preparation of chymosin. The specification does not provide additional working examples of other acid-labile enzymes whose activity may be inactivated in the presence of an acidophilic protein at a pH <2.0. Other than the examples provided for the inactivation of glucoamylase, peptidase, amylase, cellulase, phosphatase, and protease enzymatic activities in a preparation of chymosin, the specification provides no other guidance regarding other undesired proteins that may be inactivated in the presence of a desired protein that maintains activity at a pH <2.0. The specification merely provides a "laundry list" of undesired proteins that may be inactivated in the presence of a "laundry list" of desired proteins that maintain activity at a pH <2.0. One of skill in the art would recognize that enzymes that are capable of maintaining activity at a pH below 2.0 are not well known in the art and it is not common to treat proteins at a pH below 2.0 as acknowledged by applicants in Paper Nos. 9 and 10 as follows: "prior to the Applicant's discovery of the claimed invention it was not known that enzyme activity would survive

at a pH below 2.0" (page 12, lines 23 and 24 of Paper No. 9) and "the use of a pH below 2 in the context of treatment of enzymes is an uncommon practice, particularly for organic materials, such as proteins" (page 13, lines 1 and 2 of Paper No. 9 and page 3, part 8) of Paper No. 10). One of skill in the art would recognize that such treatment would inactivate most proteins and without sufficient guidance, it is highly unpredictable that the claimed method can be practiced with the broad scope of desired/undesired proteins. Based on the lack of working examples and guidance provided in the specification, a high degree of unpredictability exists in practicing the invention to obtain an active desired protein, enzyme, antibody, antigen, pharmaceutically active polypeptide, polypeptide having aspartic protease activity, pepsinogen, or pepsin while inactivating the broad scope of undesired proteins encompassed by the claims. Guidance regarding the stability of any desired protein that is stable at a pH <2.0 and any undesired protein that is unstable at pH <2.0 should be provided in order to provide one of skill in the art with a reasonable expectation of success for practicing the invention to inactivate the broad scope of recited undesired proteins from the broad scope of desired proteins as encompassed by the claims.

Because of the absence of guidance in the specification and the prior art, the lack of working examples provided in the specification, and the high degree of unpredictability as described above, undue experimentation would be required for a skilled artisan to practice the invention as broadly claimed. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

7. The rejection of claims 1-9, 12-22, 25-28, 31, and 38 under 35 U.S.C. 103(a) as being unpatentable over Laustsen (US Patent 6,080,564) in view of Larsen (WO 95/29999) and Heinsohn (US

Patent 5,215,908) is maintained for the reasons of record and the reasons described below. The rejection was fully explained in a previous Office action. Applicants argue (beginning at page 11 of Paper No. 9) one of ordinary skill in the art would not have had a reasonable expectation of success for practicing the claimed invention based on the teachings of the cited references as, applicants allege, it was not known that enzyme activity would survive at a pH below about 2.0 and it is not common to treat enzymes at such a pH. Addressing the reference of Laustsen, applicants argue Laustsen teaches away from using a pH below 2.0 as the pH used in their method was between 3.5 and 10.7. Applicants argue that, while Laustsen discusses using a pH as low as 2.0, this pH is not sufficient to inactivate glucoamylase. Addressing the reference of Heinsohn, applicants argue this reference teaches chromatographic purification of chymosin from unspecified enzymes and does not discuss glucoamylase or amylase activity or any other undesired activity and that acid pre-treatment at pH 2-3 is not sufficient to inactivate glucoamylase. Addressing the reference of Larsen, applicants argue the instant specification teaches away from the claimed method as the method of Larsen requires a further chromatography step to remove some undesired enzymatic side activities. Applicants argue (beginning at page 15 of Paper No. 9) there is no motivation to combine the teachings of Heinsohn, Larsen, and Laustsen with a reasonable expectation of success. Applicants' arguments are not found persuasive. Addressing applicants' argument regarding the absence of knowledge or uncommon practice of treating enzymes to a pH of less than 2.0, the reference of Larsen teaches that a pH as low as 0.5 can be used to convert inactive chymosin to an active form (page 10, bottom), thus pH treatment of chymosin to a pH of less than 2.0 was known in the art. Contrary to applicants' assertion, the combined references teach all limitations of the claimed invention, provide motivation for practicing the claimed invention, and provide a reasonable expectation of success of the claimed invention. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Regarding the reference of Laustsen, the examiner acknowledges applicants' argument that Laustsen does not teach using a pH below 2.0. As

stated in a previous Office action, "Laustsen does not teach using a pH of less than 2.0 to reduce undesired enzyme activities". Instead, the reference of Laustsen in combination with the others was applied to show that methods of inactivating undesired enzyme activities in the presence of a desired enzyme, in the instant case chymosin, are known in the art. It is well-known in the art that *Aspergillus* is commonly used for the recombinant production of mammalian, particularly bovine, chymosin by secretion of the produced chymosin into the culture medium (see for example the reference of Heinsohn). It is also well-known in the art that such recombinantly-produced chymosin from *Aspergillus* contains undesirable enzymes such as contaminating proteolytic activity (see for example column 3, lines 12-15 of Laustsen et al.) Laustsen et al. teaches methods of inactivating undesired enzyme activities (e.g., protease, amylase, and cellulase) by treatment with low pH. Regarding the reference of Heinsohn, only claims 8, 26, and 37 limit the undesired enzyme activity to glucoamylase. Although the claims are interpreted in light of the specification, limitations from the specification, in the instant case glucoamylase as an undesired enzyme activity, are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The examiner applied the reference of Heinsohn in combination with the other references in order to corroborate a well-known practice in the fermentation of *Aspergillus* cultures in the recombinant production of chymosin, i.e., reducing the pH of a culture medium (about 2.0 in the case of Heinsohn) in order to stop fermentation and cell growth. Regarding the reference of Larsen, the reference was applied in combination with the other references to show that, at the time of the invention, it was known in the art that chymosin could be treated with a pH as low as 0.5 and maintain enzymatic activity. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to treat an *Aspergillus* medium comprising a recombinantly produced chymosin with a pH as low as 0.5. One would have been motivated to treat an *Aspergillus* medium comprising a recombinantly produced chymosin with a pH as low as 0.5 in order to remove contaminating protease, amylase, and cellulase enzyme activities, to stop cell growth and fermentation, and optionally to convert the inactive chymosin to active chymosin, all in a single step. One would have a reasonable expectation of success for treating an *Aspergillus* medium comprising a recombinantly produced chymosin with a pH as low as 0.5 in order to remove

contaminating protease, amylase, and cellulase enzyme activities because of the results of Laustsen, Larsen, and Heinsohn. Therefore, claims 1-9, 12-22, 25-28, 31, and 38 would have been obvious to one of ordinary skill in the art.

8. The rejection of claims 10, 11, 23, 24, 29, 30, 32, 35-37, and 39 under 35 U.S.C. 103(a) as being unpatentable over Laustsen in view of Larsen and Heinsohn as applied to claims 1-9, 12-22, 25-28, and 31 above and further in view of Ward et al. (*Biotechnol* 8:435-440) is maintained for the reasons of record and the reasons described below. Applicants argue (beginning at page 14 of Paper No. 9), in addition to the arguments presented addressing the references of Laustsen, Larsen, and Heinsohn, Ward does not suggest treating the recombinantly produced chymosin at a pH of less than 2.0. Applicants argue that because the chymosin preparation of Ward et al. includes undesired enzyme activity, one of ordinary skill in the art would not be motivated to combine the cited references. Applicants' arguments are not found persuasive. The examiner acknowledges that Ward et al. do not teach treatment of their enzyme preparation at a pH below 2.0. However, Larsen et al. clearly suggests that chymosin can maintain activity even at a pH of less than 2.0. Addressing applicants' argument that one of ordinary skill in the art would not be motivated to combine the cited references because the chymosin preparation of Ward et al. includes pepstatin activity, this statement by Ward would appear to provide additional motivation to an ordinarily skilled artisan for treating the chymosin preparation at a pH *lower* than 2.0 in order to inactivate the pepstatin. Therefore, one of ordinary skill in the art would have been motivated to lower the pH to as low as 0.5 in order to inactivate the pepstatin present in the *Aspergillus* culture medium. One would have a reasonable expectation of success for inactivating the pepstatin activity at a pH lower than 2.0, as one of ordinary skill in the art recognizes that most proteins do not maintain activity at a pH less than 2.0 as acknowledged by applicants (page 12, lines 23 and 24 of Paper No. 9) and (page 13, lines 1 and 2 of Paper No. 9). Therefore, claims 10, 11, 23, 24, 29, 30, 32, 35-37, and 39 would have been obvious to one of ordinary skill in the art.

Conclusion

9. All claims are rejected. No claim is in condition for allowance.

10. The examiner requests that applicants provide a copy of all pending claims in the response to this Office action.

Rejection of claim 7 was necessitated by amendment. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 2:00 pm and from 3:30 pm to 5:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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